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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary**Application No.**

10/517,741

Applicant(s)

FOEKENS ET AL.

Examiner

Carla Myers

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 January 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1.20-22, 24, 45, 57-59, 61, 62, 67 and 77 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1.20-22, 24, 45, 57-59, 61, 62, 67 and 77 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 14, 2010 has been entered.

2. Applicant's arguments and amendments to the claims presented in the reply of January 14, 2010 have been fully considered but are not persuasive to place all claims in condition for allowance. All rejections not reiterated herein are hereby withdrawn. In particular, the previous rejection of claims 1, 20-24, 45, 57-59, 61, 62, 67 and 77 under 35 U.S.C. 112, first paragraph (new matter) is withdrawn. It has been interpreted that support for the amendment to the claims to recite that hypomethylation is indicative of a low risk for relapse and hypermethylation is indicative of a high risk of relapse is provided in Figure 19 and at para [0051] (with respect to PGPUB 20060121467) which states:

"The method according to the invention is particularly suited to the prediction of response to the aforementioned therapy in two treatment settings. In one embodiment, the method is applied to patients who receive endocrine pathway targeting treatment as secondary treatment to an initial non chemotherapeutical therapy, e.g. surgery (hereinafter referred to as the adjuvant setting) as illustrated in FIG. 1. Such a treatment is often prescribed to patients suffering from Stage 1 to 3 breast carcinomas. In this embodiment responders are defined as those who do not have a detectable relapse of the breast cancer in a specified period of time, non responders are those who relapse within said time period."

It is noted that Applicants response pointed to teachings at pages 45 and 59, last paragraph as providing support for the amendment. However, the page numbers recited by Applicant do not appear to be consistent with the page numbers of the specification that was originally filed on 12/11/04. For instance, page 59 comprises the text of Table 2 listing the sequence identifiers for genes and for oligonucleotides. Page 59 does not include any paragraphs.

3. Claims 1, 20-22, 24, 45, 57-59, 61, 62, 67 and 77 are pending and have been examined herein.

4. The following are new and modified grounds of rejection necessitated by Applicant's amendments to the claims.

Claim Rejections - 35 USC § 112 second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 20-22, 24, 45, 57-59, 61, 62, 67 and 77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1, 20-22, 24, 45, 57-59, 61, 62, 67 and 77 are indefinite over the recitation of "selected from the group consisting essentially of" and "selected from the sequence group consisting essentially of " (see claim 1, line 10; claim 20, line 2; claim 45 line 15; claim 59, line 4; claim 62, line 11 and claim 77, line 3) because the claims recite an improper format for a Markush group. Claims which recite members of a

Markush group must be 'close-ended'. It is noted that The MPEP (2111.03 – Transitional phrases) indicates that:

A 'consisting essentially of' claim occupies a middle ground between closed claims that are written in a 'consisting of' format and fully open claims that are drafted in a 'comprising' format." PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising."

Thereby, the phrase "consisting essentially of" is not "close-ended." Further, it is noted that MPEP 2173.05(h) states that "It is improper to use the term "comprising" instead of "consisting of" when reciting a Markush group. Ex parte Dotter, 12 USPQ 382 (Bd. App. 1931)."). It is thereby also improper to recite the term "consisting essentially of" to when reciting a Markush group since "consisting essentially of" is not a closed-ended term. This rejection may be overcome by amendment of the claim to recite "selected from the group consisting of".

Response to Remarks:

In the response, Applicants state that the rejection has been overcome by amendment of the claims to recite "consisting essentially of" in place of "consisting of essentially." This argument is not persuasive because, as discussed in detail above, claims which recite members of a Markush group must recite a group that is 'close-ended.' Because the phrase "consisting essentially of" may include other embodiments or members that do not materially affect the basic and novel features of a group or its members, such language is not 'close-ended.' Thereby, the rejection is maintained.

B. Claims 1, 20-22, 24, 45, 57-59, 61, 62, 67 and 77 are indefinite. The claims are drawn to methods for predicting the responsiveness of a human subject with breast cancer to a therapeutic treatment or an adjuvant therapeutic treatment. The claims recite a final step of determining a genomic DNA methylation status. The claims also recite a wherein clause that indicates that "hypomethylation is indicative for a low risk for relapse while hypermethylation is indicative for a high risk for relapse" and "wherein predicting responsiveness of the subject to the adjuvant therapeutic treatment is afforded." The claims do not, however, recite an active process of predicting responsiveness to therapeutic treatment. The recitation regarding the risk of relapse is not equivalent to predicting responsiveness to therapeutic treatment since relapse is not of an equivalent scope as the general/broad concept of responsiveness to therapeutic treatment. Moreover the claims do not recite how the method affords the prediction of responsiveness to therapeutic treatment. Thereby, it is not clear as to whether the claims are intended to be limited to only methods that determine the genomic DNA methylation status, or methods which determine risk of relapse, or methods which predict overall responsiveness to therapeutic treatment. If the claims are intended to be limited to methods that afford predicting any type of responsiveness to therapeutic treatment, the claims omit the essential process steps that permit such a determination since the claims evaluate only risk of relapse and not overall responsiveness to therapeutic treat of determining that the test compound does or does not have anti-neoplastic activity. See MPEP § 2172.01. Additionally, if the claims are intended to be limited to methods which predict risk of relapse, it is unclear as to whether the claims

broadly encompass determining risk of any relapse or risk of relapse following adjuvant therapy. The claims do not necessarily require actually treating the subject with adjuvant therapy since the claims include obtaining a sample prior to adjuvant therapy. Note that MPEP 2773.02 states that if the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand how to avoid infringement, a rejection of the claim under 35 USC 112, second paragraph, is appropriate. This rejection may be overcome by amendment of the claims to recite a "method for determining if a human subject having an estrogen receptor-positive breast cancer has a high risk of relapse or a low risk relapse following adjuvant therapeutic treatment comprising...wherein hypomethylation of SEQ ID NO: 83 or the complement thereof is indicative of a high risk for relapse following adjuvant therapeutic treatment and hypermethylation of SEQ ID NO: 83 or the complement thereof is indicative of a low risk of relapse following adjuvant therapeutic treatment."

Claim Rejections - 35 USC § 112 – Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 20-22, 24, 45, 57-59, 61, 62, 67 and 77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn to methods for predicting the responsiveness of a human subject with breast cancer to an adjuvant therapeutic treatment comprising determining the genomic methylation status of at least one CpG dinucleotide in the PITX2 gene sequence of SEQ ID NO: 83 or the complement thereof, wherein hypomethylation is indicative for a low risk for relapse while hypermethylation is indicative for a high risk for relapse, and wherein predicting responsiveness of the subject to the adjuvant therapeutic treatment is afforded.

The claims encompass methods which predict responsiveness to any type of adjuvant therapy that targets the estrogen receptor pathway or is involved in estrogen metabolism, production or secretion. Thereby, the claims encompass determining responsiveness to a very wide range of drugs (antisense drugs, ribozymes, antibody therapy, organic and inorganic compounds), which differ in their structure and mechanism of action.

The claims also include methods in which any biological sample from a subject is analyzed for CpG methylation in a PITX2 gene sequence. The claims thereby include

the analysis of methylation of CpGs of the PITX2 gene obtained from any cellular or any acellular sample containing PITX2 nucleic acids, including such diverse samples as plasma/serum, such as ductal lavage fluid, nipple aspiration fluid, urine, feces, tears or saliva, skin tissue, liver tissue, heart tissue, etc. The claims also specifically include analyzing cell lines generated from a subject (see claim 77).

The claims include analyzing the methylation status of any one or more CpG dinucleotides in the 6343bp sequence of SEQ ID NO: 83.

Moreover, the claims broadly recite determining the genomic DNA methylation status "wherein predicting responsiveness of the subject to the therapy is afforded." While the claims recite the hypomethylation is indicative for a low risk for relapse while hypermethylation is indicative for a high risk for relapse, the claims do not recite how the method affords the prediction of responsiveness. The claims do not set forth a relationship between relapse and responsiveness or clarify how the method accomplishes the goal of predicting responsiveness. Thereby, the claims encompass predicting responsiveness based on either the presence or absence of methylation at any one or more CpG dinucleotides or based on either hypermethylation or hypomethylation of any one or more CpG dinucleotides, or based on any other parameter or result. The claims also encompass predicting any type of responsiveness to therapeutic treatment, include such diverse responses as nausea, weight gain, weight loss, sleeplessness, anxiety, susceptibility to influenza, change in tumor size, occurrence of metastasis, etc.

Nature of the Invention

The claims encompass predicting responsiveness to therapy breast cancer by assaying for the methylation status of a CpG dinucleotide in the PITX2 gene. The invention is in a class of inventions which the CAFC has characterized as "the unpredictable arts such as chemistry and biology" (Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification (page 11) teaches that "The gene PITX-2 (NM_000325) encodes a transcription factor (PITX-2) which is known to be expressed during development of anterior structures such as the eye, teeth, and anterior pituitary. Although the expression of this gene is associated with cell differentiation and proliferation it has no heretofore recognized role in carcinogenesis or responsiveness to endocrine treatment."

In Example 1 (page 40), the specification teaches methylation analysis of genes from 200 patients, including the PITX2 gene. The sequence of the primers and the gene sequence analyzed are set forth in Tables 1 and 2. Regarding the elected invention, the specification teaches amplification of a 408 bp region of the 6343bp sequence of SEQ ID NO: 83 using the primers of SEQ ID NO: 1055 and 1056 (page 54). Microarray analysis was performed to determine the CpG methylation status of the amplification products. The specification does not clearly set forth the source of the nucleic acids that were analyzed. The data obtained from Example 1 (dataset 1) is presented in Figures 5 to 12. These figures are characterized on page 34 as showing the methylation status of two classes of tissues, although the source of the tissue is not provided. Also,

while page 40 of the specification states that 200 patients were analyzed, page 40 does not characterize the patients in terms of their type of disease (i.e., type of breast tissue cell proliferative disorder), type of treatment, age, gender etc. In characterizing Figure 1, the specification (page 32) indicates that the figure shows the model of endocrine treatment of stage 1-3 breast cancer wherein primary treatment was surgery followed by adjuvant therapy with Tamoxifen. With respect to Figure 1, responders are characterized as "remaining below the limit of detectability for the duration of the observation" and non-responders are characterized as having a period of disease free survival followed by relapse when the carcinoma reached a level of detectability (pages 32-33). However, the specification does not teach whether this information applies to all examples provided in the specification. Therefore, with respect to the examples provided in the specification, the information regarding the characterization of the subjects (type, stage etc of the disorder), drug used for treatment, and criteria for defining responders versus non-responders is unclear.

For a "Data set 1", responders or non-responders to Tamoxifen as an adjuvant surgery following surgery were analyzed. The source of the samples analyzed is not stated (e.g., breast, skin, cell lines, blood). Figures 5 and 6 list a p value for PITX2 as 0.995. Page 34 characterizes this figure as showing p values which are the probabilities that the observed distribution occurred by chance. This information appears to indicate that PITX2 CpG methylation was not associated with response or lack of response to tamoxifen adjuvant therapy following surgery. The figures are also characterized as showing the positions of specific CpGs in the gene, and as showing degrees of

methylation with light colors representing low levels of methylation and dark colors representing high levels of methylation. However, the figures do not identify the particular nucleotide position of the CpGs within the PITX2 gene or the amplified fragment of the PITX2 gene. Thereby, it cannot be ascertained which particular CpGs show a difference in methylation status between responders and non-responders.

The specification at pages 44-45 discusses the results associated with a "Data set 2: Adjuvant setting." It is stated that every CpG was put into a Cox proportional hazard model with predictive factors of N-stage and tumor size. The specification states that the best marker was the PITX2 gene. However, the specification fails to state what PITX2 is a marker of. For example, is PITX2 the "best marker" of survival, N-stage, tumor size, response to treatment? It is also stated that oligonucleotide 3522:2087 gives information about survival time independent of nStage. However, the specification does not characterize the identity of oligonucleotide 3522:2087. Also, in this example, the number of patients analyzed is not provided, nor are the patients characterized with respect to their disorder, treatment, age, sex etc. Moreover, survival time, N-stage and tumor size are considered to be prognostic factors and are not equivalent to determining the responsiveness to therapy.

At page 45, the specification discusses a "Data set 4: Metastatic setting." While the subjects are characterized as being treated with tamoxifen, the subjects are not characterized with respect to their disorder. It is stated that individual CpGs measured were combined for each gene. However, the region of the PITX2 gene analyzed, and thereby the CpGs analyzed is not clearly stated. Figure 16 is characterized as showing

the best 11 amplicates of the data obtained in Dataset 4. The PITX2 gene is not included as one of the 11 best amplicates.

At page 46, the specification discusses a "Data set 4: Adjuvant setting." It is stated that the results are provided in figures 17-21 as Kaplan-Meier estimated disease-free survival curves. PITX2 is said to have a p value of $p = 3e-04$. The results for PITX2 are provided in Figure 19. The number of subjects analyzed is listed as 278. However, the subjects are not clearly characterized with respect to their disorder or as to whether N is the number of each of the responder and non-responder subjects or N is the combined number of responder. Also, the X and Y axis of this figure are not characterized. It appears that the figure intends to compare the proportion of subjects that are responders or non-responders with disease-free survival over the period (months?) recited in the X axis. The specification (page 46) states that "the mean methylation over all oligo-pairs for that amplicate was calculated and the population split into equal sized groups according to their mean methylation values." However, the specification does not clearly characterize the identity of the PITX2 amplification products that were analyzed. Figure 19 is characterized as showing that the upper line constitutes responders and the lower line constitutes non-responders. Thereby, if the Y axis is intended to be probability of survival and the X axis is survival time, Figure 19 indicates that "+" methylation subjects responded to adjuvant treatment and had a better survival as compared to "-" methylation subjects. However, the specification does not clearly characterize the "adjuvant setting" for data set 4 – i.e., whether the adjuvant treatment is tamoxifen or some other unspecified adjuvant therapy

Regarding Data set 3, the specification (page 46) teaches that methylation of several genes were associated with response to tamoxifen and include STMN1, SFN, S100A2, SYK, GRIN2D, PSA, COX7A2L, VTN, and PRKCD. PITX2 is not included in this list. At page 48, the specification concludes that: "we have shown for the first time that an epigenetic profile based on the CpG island DNA methylation status of promoter regions of just five genes can predict the likelihood of therapy response in patients with ER-positive advanced breast cancer treated with tamoxifen therapy." The 5 "independent predicting genes" are listed on page 67 as PSA-t, STMN1, GRIN2d, TGFB2 and S100A2. PITX2 is not included in this list.

Accordingly, the information provided in the specification is not sufficiently complete or detailed to allow one to interpret the information. Complete information is not provided in the examples regarding each of the type of disorder present in the subjects, the source of the sample analyzed (primary breast tissue or other types of primary tissue, cell lines, blood etc), the age, sex, gender and number of subjects analyzed, the type of treatment (primary or adjuvant), drug(s) used for therapy, and the criteria used to define responsiveness to therapy (other than survival time). Also, the specification does not clearly characterize which particular CpGs in the PITX2 gene, and particularly within the 408bp region of SEQ ID NO: 83, are associated with an increase or decrease in methylation and whose methylation status is correlated with response to adjuvant treatment. Accordingly, insufficient information is provided in the specification to allow the skilled artisan to predictably extrapolate the results obtained therein to predict the response of a human breast cancer patient to any adjuvant

treatment by assaying for the methylation status of any one or more CpGs in the PITX2 sequence of SEQ ID NO: 8.

The Predictability or Unpredictability of the Art :

The art of determining an association between methylation status and response to therapy is highly unpredictable. While methylation status is known to effect gene expression, there is no clear art recognized association between methylation status and response to any therapy for any breast tissue cell proliferative disorder.

The unpredictability of predicting responsiveness to therapy by assaying for PITX2 methylation at any CpG dinucleotide is highlighted by the teachings in the following post-filing date art, of which the present inventors are co-authors.

In particular, Martens et al (Cancer Research. 2005. 65(10): 4101-4107) teaches the results of a study of the methylation status of 117 genes, including the PITX2 gene, in 200 steroid hormone receptor responsive tumors in patients who received tamoxifen as first-line treatment for recurrent breast cancer. Martens did not observe an association between methylation status of PITX2 (see Supplemental Tables 1 and 2).

The findings of Martens were discussed by Nimmrich et al (Breast Cancer Research and Treatment. 2008. 111:429-437). With respect to the Martens reference, Nimmrich states that "earlier work from our group in clinical specimens did not find *PITX2* DNA-methylation to be associated with intrinsic tamoxifen resistance in metastatic breast cancer" (page 430). At page 434, Nimmrich states that in the previous retrospective study of Martens, "we did not find DNA-methylation of PITX2 of the primary tumor to be associated with tamoxifen response (given as a first-line single

endocrine agent) in metastatic breast cancer. Nimmrich studied DNA-methylation of the PITX2 gene in untreated lymph node-negative hormone receptor positive breast cancer patients. The authors found that hypermethylation of PITX2 was associated with a poor prognosis and disease progression in these patients. Nimmrich also clarifies the distinction between a marker that is prognostic and markers that are predictive of response to treatment, stating that "a prognostic factor is not necessarily also a predictive marker, or vice versa" (page 434). Nimmrich also acknowledges that differences in methylation results may occur between early stage and advanced breast cancer due to the differences in tumor biology (page 434). The teachings of Nimmrich support the unpredictability of extrapolating the results obtained with one type of breast tissue proliferative disorder to other types of breast tissue proliferative disorders (e.g., early stage breast cancer as compared to late stage, metastatic breast cancer), and with one type of therapy to other types of therapy (e.g., primary treatment with tamoxifen as compared to adjuvant treatment of recurrent cancer with tamoxifen).

The claims further encompass methods in which any sample type is analyzed for the methylation status of CpGs. Thereby, the claims encompass analyzing such diverse samples as serum/plasma, urine, brain tissue, saliva etc. However, it has not been established that changes in methylation status in subjects having proliferation diseases occur in all tissues and cells and in acellular nucleic acids. The fact that gene expression may vary significantly between tissue types, and thereby methylation patterns may also vary between tissue types, is well accepted in the art. However, no information is provided in the specification regarding the methylation pattern of the

PITX2 gene in blood samples, spinal cord, lymphatic fluid, urine, feces, or tears etc from patients having a breast tissue proliferative disorder. Also, no information is provided regarding the level of methylation of extracellular PITX2 nucleic acids in biological fluids, such as serum or plasma. In the absence of evidence showing a change in methylation status in a representative number of diverse sample types, it is highly unpredictable as to whether the results obtained in one sample type, such as primary breast tissue, can be extrapolated to other tissue types.

It is also highly unpredictable as to whether cell lines generated from patient samples can be analyzed as predictive of response to therapy (as is specifically encompassed by claim 77). It is well accepted that the genetic alterations which occur in cell lines are not necessarily reflective of the genetic changes which occur *in vivo*. For instance, Dermer, G.B. (Bio/Technology (1994) 12: 320) states that "The cell lines in which cancer is usually studied are unsuitable for the job. They do not mimic conditions in the human body." Dermer concludes that "Petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease." Since the results obtained *in vitro* in cell lines cannot be extrapolated to *in vivo*, knowledge that a gene is methylated or not methylated in a cell line does not allow one to conclude that this gene is associated with response to treatment *in vivo*.

As stated on page 11 of the specification, the function of the PITX2 gene in the occurrence of cancer is currently unknown. As recently as 2008, Nimmrich states that "(f)rom a biological point of view, the role of PITX2 DNA-methylation and cancer is unknown" (page 435, col. 1). The lack of a clear structure – function relationship

between PITX2 methylation and cancer, and particular response to treatment of cancer with drugs that target the estrogen receptor, further compounds the unpredictability of extrapolating results obtained from humans to other organisms. In view of the variability in gene expression levels and thereby expected variability in methylation patterns between organisms and the lack of a structure-function relationship between methylation of the PITX2 gene and response to treatment, insufficient information is provided in the specification to establish that any results obtained in the specification regarding PITX2 methylation in humans can be extrapolated to a representative number of diverse non-human organisms.

It is further unpredictable as to whether any single CpG or any combination of any CpGs in any region of the PITX2 gene sequence of SEQ ID NO: 83 can be analyzed for the methylation status as indicative of response to treatment. The claims do not require any type of comparison step with a control, non-cancer or non-responsive sample, and thereby include methods in which the presence or absence of methylation at a single CpG is detected as predictive of response. However, the specification has not established such an association between any single CpG and response to any treatment. Further, the results in the specification appear to be limited to a 408bp region amplified using the primers of SEQ ID NO: 1056 and 1055 (page 54). It is well known in the art that different regions of a gene may be methylated in cancer tissues and in normal tissues. Thereby, the occurrence of any one methylated CpG alone is not necessarily predictive of response to treatment. Further, the effect of methylation may vary depending on the location of the methylated CpG. For example, methylation of

CpGs present in the promoter region of a gene may alter gene expression, whereas methylation of CpGs in coding sequences of a gene may not effect gene expression. The unpredictability of applying methylation results to the prediction of a phenotype is supported by the teachings of Ushijima (Nature Reviews. 2005. 5: 223-231). Ushijima teaches that "interpretation of differential methylation has proven difficult because the significance of methylation alterations depends on the genomic region, and functions of the CpG islands at specific sites have not been fully clarified" (see abstract). Ushijima teaches that both hypermethylation and hypomethylation are associated with the occurrence of cancer (page 223). Ushijima (page 223) also teaches that "it has become recognized that methylation in cancer cells frequently occurs in CGIs outside promoter regions, which do not repress gene transcription, and also in promoter CGIs of genes that cannot be regarded as tumour-suppressor genes. Even in normal cells, methylation of specific CGIs frequently occurs. Therefore, to identify novel tumour suppressor genes silenced in cancer cells by CGI methylation it is necessary to carefully select the particular CGIs to be included in the analysis."

Quantity of Experimentation and Amount of Direction or Guidance Provided by the Specification:

The specification does not provide any specific guidance as to the types of cells or tissues, other than primary breast tissue, which one would be expected to show a change in methylation status in subjects having breast cancer. One cannot determine a priori which tissues or biological fluids will contain PITX2 nucleic acids showing an

altered methylation pattern as predictive of response to therapy. Such information can only be obtained through experimentation.

The specification does not provide sufficient guidance as to how to determine which particular CpGs in the PITX2 gene sequence of SEQ ID NO: 83 are to be analyzed as predictive of response to therapy. The claims encompass methods in which any single CpG or any combination of CpGs in any coding or non-coding region of the PITX2 gene are analyzed for their methylation status to thereby "afford" prediction of responsiveness to therapy. The claims also include analyzing a 6343 bp region of the PITX2 gene recited in SEQ ID NO: 83, or any sequence comprising a portion of SEQ ID NO: 83 or any sequence having any level of complementarity thereto (e.g., 20% or 10% complementarity). However, it appears that the specification analyzed a region consisting of only 408 nucleotides of SEQ ID NO: 83. While Figures 5 and 6 are characterized as illustrating the CpGs in the PITX2 gene that have an increased or decreased level of methylation, these figures do not clearly identify the location of particular CpGs or combinations of CpGs that should be analyzed in order to predict response to therapy. It is also unclear as to whether an increase in methylation (relative to a control, non-cancer sample?) is associated with response to therapy or is associated with a lack of response to therapy. Thereby, insufficient guidance is provided in the specification as to how to interpret the results obtained from determining the methylation status of any one or more CpGs in any portion of the PITX2 gene to thereby predict responsiveness to therapy.

The specification does not provide sufficient guidance as to how to extrapolate the findings provided therein to any adjuvant therapy or to any type of response to adjuvant therapy. It appears that the teachings in the specification may be limited to an analysis of survival time of human breast cancer patients following treatment with tamoxifen. In such a case, it is highly unpredictable as to whether the results obtained with tamoxifen can be extrapolated to other adjuvant therapies. The specification does not clarify the mechanism by which methylation of PITX2 effects survival of breast cancer patients to tamoxifen. Thereby, one cannot predict how methylation of PITX2 will effect the survival of breast cancer patients treated with other adjuvant therapies. Further, one cannot reasonably predict how PITX2 methylation will effect other types of response to treatment, such as a decrease in tumor bulk, risk of metastasis, risk of side effects, etc.

Extensive experimentation would be required to identify additional tissues in which PITX2 methylation is correlated with a type of responsiveness to treatment with a drug that targets an estrogen receptor pathway, estrogen metabolism, production or secretion. While methods for determining CpG methylation status are known in the art, such methods provide only the general guidelines that allow researchers to randomly determine if particular CpGs or regions of a gene containing CpGs are methylated. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional organisms and tissues/fluids and particular

CpGs in which an altered CpG methylation status will be correlated with response to therapy that targets estrogen receptors.

Working Examples

The specification does not specifically provide any working examples in which response of a patient having a breast cancer is predicted by assaying for the methylation status of any one or more CpG dinucleotides in the PITX2 sequence of SEQ ID NO: 83.

The specification does not provide any working examples in which response to therapy is predicted by assaying cell lines, blood samples, urine samples, plasma samples, etc for the methylation status of CpG dinucleotides.

The specification does not provide any working examples in which response to any non-tamoxifen therapy is predicted wherein the drug is one that targets any component of the estrogen receptor pathway or one that is involved in estrogen metabolism, production or secretion.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the

art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the present application, the specification does not provide sufficient information regarding the study population in order to allow one to extrapolate the findings obtained therein to the general population. As discussed above, the examples set forth in the specification do not clearly characterize each study group with respect to the type of disorder of the subjects studied, the type of therapy employed, whether the therapy was primary or adjuvant, the criteria for defining a responder versus a non-responder, the CpG dinucleotides or combination of dinucleotides which showed a change in methylation status, whether the change in methylation status was an increase or decrease in methylation, and the type of sample that was analyzed. Moreover, the teachings in the specification and post-filing date art appear to indicate that while the PITX2 gene may be a prognostic factor, the methylation status of PITX2 is not predictive of any type of response to any type of adjuvant therapy.

Further, if it can be established that the data in the specification shows that methylation status of PITX2 is correlated with response to treatment, the claims would not be considered to bear a reasonable correlation to the scope of enablement because the claims encompass predicting responsiveness to any therapy that targets an estrogen receptor pathway component in any subject having any breast tissue cell proliferative disorder by assaying for methylation of any one or more CpG dinucleotides

in SEQ ID NO: 83. Further, the claims do not bear a reasonable correlation to the scope of enablement because the specification does not teach a change in PITX2 methylation status in a representative number of diverse tissue and fluid and acellular DNA samples encompassed by the claims. In view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Response to Remarks:

In the response, Applicants state that Example 1, Data set 2 (adjuvant therapy) supports the claimed correlation between PITX2 methylation status and response to therapeutic treatment.

This argument is not convincing because the information in data set 2: adjuvant therapy (pages 44-45 of the specification) does not establish the enablement of a method for predicting any type of responsiveness to any adjuvant therapy in a human breast cancer patient that is estrogen receptor positive by assaying for the methylation status of any single CpG in SEQ ID NO: 83.

Page 45 states: "Every CpG was put into a Cox proportional hazard model together with the known predictive markers N-stage and tumour size. The best marker was the gene PITX 2...This shows that 3522:2087 gives information about survival time independent of nStage. The tumour size has no significant predictive power for expected survival time."

Yet, the specification does not appear to disclose what constitutes oligonucleotide 3522:2087. In response to this Office action, if Applicants chose to rely on this data, Applicants should point to a specific teaching in the specification which clarifies the identity of oligonucleotide 3522:2087 or provide declaratory evidence establishing the identity of this oligonucleotide so that the results presented at pages 44-45 can be properly interpreted. It remains unclear as to the relationship between oligonucleotide 3522:2087 and SEQ ID NO: 83. Further, it remains unclear as to how the results in the specification can be practiced without undue experimentation because the specification does not teach that the methylation status of only one of the possible CpGs in SEQ ID NO: 83 can be determined as indicative of any type of response to any adjuvant therapy that targets an estrogen receptor pathway. The results at pages 44-45 appear to be based on the analysis of each CpG in oligonucleotide 3522:2087, rather than on any one single CpG. Also, other portions of the specification appear to be limited to an analysis of the methylation status of each of the CpGs in the 408bp region amplified using the primers of SEQ ID NO: 1056 and 1055 (page 54). The response does not point to any particular teachings in the specification or any other evidence that establishes that the methylation status of any single CpG in the 6343bp sequence of SEQ ID NO: 83 is correlated with risk of relapse following adjuvant therapy or correlated with any type of responsiveness to adjuvant therapy.

Further, the response should clarify the identity of the adjuvant therapy used to obtain the results set forth on pages 44-45. If data set 2 is limited to the adjuvant therapy of tamoxifen, then the response should acknowledge this fact and should

explain why the findings obtained with tamoxifen can be extrapolated to all other types of adjuvant therapy.

The response states that "the specification at page 40 discloses that the number of analyzed patients is specified with 200. Moreover, the application refers to breast cancer or breast proliferative disorders, and as will be appreciated in the art, the analyzed patients are human females."

However, the response fails to point to a specific teaching in the specification which indicates that the 200 subjects analyzed were female human subjects having breast cancer. Rather, page 40 of the specification states "samples from 200 patients were analyzed." This teaching also does not clearly indicate that in each data set from Example 1, 200 subjects were analyzed. This point is relevant since Figure 19 appears to indicate that 278 subjects were analyzed (i.e., "N= 278"). The response does not clarify the relationship between the 200 subjects referred to at page 40 and the disclosure of "N=278" in Figure 19. Moreover, the response does not clarify if the 200 subjects had estrogen receptor-positive breast cancer, as required by the claims, or had estrogen-negative breast cancer, or if the 200 subjects included equivalent numbers of estrogen-positive and estrogen-negative breast cancer patients or if the 200 subjects had some other type of breast proliferative disorder. Note also, that breast cancer does in fact occurred in male subjects, and the present claims include both male and female subjects, yet the response does not point to a particular location in the specification wherein it is disclosed that the patients are females. Applicants also appear to be relying on the fact that the specification "refers to breast cancer and breast proliferative

disorders" in order to support a conclusion that the 200 subjects had breast cancer. However, since the specification discussed the general concept of any breast proliferative disorder, as acknowledged in Applicant's response, it cannot be conclusively determined that the 200 subjects referred to at page 40 necessarily had breast cancer, as opposed to some other unspecified breast proliferative disorder.

The response states that "(w)ith regard to the mutually contradictory results between Martens et al., and Nimmrich et al., Applicants point out that Martens et al., was not in the adjuvant setting, and thus respectfully maintain that the Examiner has not presented any reasonably basis why these two post-filing references should preclude patentability of the presently amended claims, which are supported by Applicants' specification."

This argument is not persuasive because the findings of Martens do establish the unpredictability in the art. Again, Martens teaches the results of a study of the methylation status of PITX2 gene, in 200 steroid hormone receptor responsive tumors in patients who received tamoxifen as first-line treatment for recurrent breast cancer. Martens did not observe an association between methylation status of PITX2 (see Supplemental Tables 1 and 2). Martens (page 4101, col. 2) teaches that "(f)rom a biological point of view, however, first-line single agent endocrine therapy in patients with recurrent breast cancer is an excellent setting to study response to therapy because it is less subject to prognostic influences unavoidably present when a similar study would be done in the adjuvant setting." Clearly, if the results obtained with Martens regarding response to tamoxifen in recurrent breast cancer are opposite those

results purported by Applicants for adjuvant tamoxifen therapy in unspecified breast cancer patients, then it is highly unpredictable as to whether the results asserted in the specification could be extrapolated to any type of response to any type of adjuvant therapy. Applicant's response does not explain why one would readily expect that the results would be different between a first-line response to tamoxifen in recurrent breast cancer as compared to response to adjuvant tamoxifen therapy in breast cancer, while maintaining that the results obtained with adjuvant tamoxifen therapy can be extrapolated to any type of responsiveness to any type of adjuvant therapy in breast cancer or recurrent breast cancer.

In discussing the variation in results reported therein as compared to those of Widschwendter, Martens (page 4106, col. 1) states that the "reasons for the differences between that study and ours could be manifold including differences in study design (adjuvant versus first-line treatment), in the CpG sites analyzed, in the technology used, or in size or composition of the tissue collections used. Due to the heterogeneity of the cohorts and the likely confounding influence of steroid hormone receptor status, and different treatment modalities, the results of the study of Widschwendter et al are difficult to interpret." Thus, Martens teaches that while it is possible that there may be a difference in results between adjuvant therapy and first line therapy, it is equally possible that any differences in results may be due to a number of other factors including the identity of the CpG sites analyzed, the tissue sample analyzed and the steroid receptor status of the breast cancer analyzed. Martens notes that the absence of such information makes the results difficult to interpret. This is similar to the present

situation wherein the specification does not provide sufficient information regarding the source of the tissue analyzed, the CpGs analyzed, the steroid receptor status of the patient, or the adjuvant therapy that was used to obtain the data provided in data set 2 and 4.

The response asserts that undue experimentation would not be required to practice the claimed invention. It is asserted that there is no requirement for a disclosure of every species within a genus. It is also argued that routine experimentation is permissible and that methods of high-throughput methylation assays could be used to determine the methylation status within the PITX2 gene. Applicants conclude that they are entitled to claims that are commensurate in scope with that which one of skill in the art could obtain by virtue of what Applicants have disclosed.

These arguments have been fully considered but are not persuasive. Applicants arguments essentially indicate that it would be within the skill of the art to assay for methylation of PITX2 gene sequences. Applicants arguments do not establish that the results of performing such assays would be predictable and would allow the artisan to practice a method of predicting any type of response to any type of adjuvant therapy in a breast cancer patient by determining the methylation status of any CpG in a PITX2 gene sequence of SEQ ID NO: 83 obtained from any tissue or fluid sample of an estrogen receptor positive breast cancer patient. While determining the methylation pattern of a gene is within the skill of the art, it is highly unpredictable as to the identity of particular methylation patterns that are associated with response to therapy. As discussed above, the specification does not provide sufficient information regarding the

study presented therein to permit one to determine if methylation of particular CpG sequences in the PITX2 gene sequence of SEQ ID NO: 83 are hypomethylated or hypermethylated in male or female patients having a particular type of breast cancer (estrogen receptor positive or estrogen receptor negative) and showing an increase or a decrease risk of relapse following a particular type of adjuvant therapy or showing any type of responsiveness to an adjuvant therapy. Further, the Office action establishes the unpredictability in the art of extrapolating the findings obtained with response to one type of adjuvant therapy to other types of adjuvant therapy, with the findings obtained with one tissue sample type to other tissue sample types and other cellular and acellular sample types, and with the results obtained regarding methylation status of one particular gene sequence (e.g., the 408bp promoter region of SEQ ID NO: 83 amplified using the primers of SEQ ID NO: 1056 and 1055) to other PITX2 gene sequences and particular CpG dinucleotides within other PITX2 gene sequences.

MPEP 2164.08(b) discusses inoperative subject matter which fall within the scope of a claim. The MPEP states the standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative. In the present situation, it is maintained that the skilled artisan would not be able to determine which embodiments were inoperative or operative. The identity of particular CpG sites that are correlated with particular types of responsiveness to particular adjuvant therapies is unpredictable and can only be determined through extensive experimentation. Accordingly, it is maintained that in view of the high level of unpredictability in the art, and the lack of disclosure in the

specification and in the prior art, it is maintained that it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 20-22, 24, 45, 57-59, 61, 62, 67, and 77 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6-7, and 11-16 of copending Application No. 10/582,705 in view of Berlin et al (WO 02/77272, 03 October 2002). Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '705 are both inclusive of methods of predicting the response of a subject having a cell proliferative disorder of the breast tissue to a treatment comprising

determining the methylation status of one or more CpG positions within the PITX2 gene to thereby predict a subject's response to adjuvant therapeutic treatment. While the claims of '705 do not define the treatment as one that target the estrogen receptor pathway or that are involved in estrogen metabolism, production or secretion, when read in light of the specification of '705 it is clear that the treatment is intended to specifically include treatments that target the estrogen receptor pathway and treatments that are involved in estrogen metabolism, production or secretion, and particularly include treatment with tamoxifen (see paras [0191], [0378] and [0476] of the PGPUB for '705, i.e., 20080254447).

Further, while the claims of '705 do not specifically recite that the target sequence of the PITX2 gene comprises SEQ ID NO: 83, the claims of '705 do include analyzing the methylation status of any region in the PITX2 gene. However, Berlin et al disclose the promoter region of the PITX2 gene (SEQ ID NO: 47 therein) which consists of the same sequence as present SEQ ID NO: 83. Berlin teaches analyzing the methylation status of this PITX2 sequence to determine a correlation between the methylation status and the occurrence of hematopoietic cell proliferative disorders.

Since the claims of '705 encompass analyzing the methylation status of any CpG sequence in the PITX2 gene as indicative of response to adjuvant therapy in human breast cancer patients and because Berlin specifically teaches analysis of the methylation status of a PITX2 gene sequence, including the promoter region, which consists of a sequence identical to present SEQ ID NO: 83, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the

method claimed in '705 so as to have specifically analyzed the CpGs present in SEQ ID NO: 83 because methylation of these CpGs were known to occur in proliferative disorders and because the ordinary artisan would have recognized that the PITX2 gene sequence encompassed by the claims of '705 necessarily included the PITX2 promoter sequence of SEQ ID NO: 83 disclosed by Berlin et al.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Remarks:

In the response, Applicants state that the claims have been amended to recite that the method is one which determines the methylation status of a CpG in SEQ ID NO: 83 or in the complement thereof. IT is asserted that the claims of '705 recite only the analysis of SEQ ID NO: 23.

To the extent that this argument applies to the present grounds of rejection, it is noted that Berlin has been cited as teaching determining the methylation status of a region of the PITX2 that includes the promoter region and which consists of a sequence that is identical to present SEQ ID NO: 83. As discussed above, Since the claims of '705 encompass analyzing the methylation status of any CpG sequence in the PITX2 gene as indicative of response to adjuvant therapy in human breast cancer patients and because Berlin specifically teaches analysis of the methylation status of a PITX2 gene sequence, including the promoter region, which consists of a sequence identical to present SEQ ID NO: 83, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method claimed in

'705 so as to have specifically analyzed the CpGs present in SEQ ID NO: 83 because methylation of these CpGs were known to occur in proliferative disorders and because the ordinary artisan would have recognized that the PITX2 gene sequence encompassed by the claims of '705 necessarily included the PITX2 promoter sequence of SEQ ID NO: 83 disclosed by Berlin et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634